Longer-term results, z scores, and decision nomograms for treatment of the ascending aorta in 1693 bicuspid aortic valve operations

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ABSTRACT

Objective: This study aims to fine-tune the decision making for ascending aorta treatment in bicuspid aortic valve surgery.

Methods: A total of 1693 patients with a primary indication for aortic valve surgery were investigated retrospectively with respect to a multifactorial decision-making policy including the z score and the clinical outcome in relation to different techniques for ascending aorta treatment (no intervention n = 1116; intervention n = 577 either by ascending aorta replacement n = 404 or aortoplasty n = 173). Follow-up was 99.5% complete (mean 7.0 ± 4.4 years, range 0–17.7 years, 11,895 patient-years).

Results: Hospital mortality was 1.2% for the no-intervention group and 0.9% for the intervention group and was not different between groups ($P = .629$). Survival compared with the adjusted normal population was lower for both groups (no intervention: $P < .001$) but not by such a great margin for the intervention group ($P = .27$). Determinants for death were not related to the ascending aorta treatment. Aortoplasty led to significantly more reoperations ($P = .002$). The z score thresholds for intervention on the ascending aorta were greater for younger patients, intervention was more liberal in young age, depicted in nomograms.

Conclusions: In our study, ascending aorta intervention could be performed with low hospital mortality and obviously did not add to the overall mortality compared with no intervention. Ascending aorta replacement was the most definite intervention. The multifactorial decision for ascending aorta intervention including the z score of the ascending aorta was more liberal in younger patients compared to the simple aortic size guidelines and provided excellent results. However, generalizability needs further data. (J Thorac Cardiovasc Surg 2018;155:549–59)

Age and z score-based decision thresholds for ascending aorta intervention in bicuspid aortic valve surgery.

Central Message

Multifactorial decision for aortic intervention during bicuspid aortic valve surgery including the z scores was more liberal in patients of younger age with excellent short- and longer-term results.

Perspective

Currently, simple aortic size criteria determine ascending aorta repair in bicuspid aortic valve surgery. However, normal aortic size increases with patients' age and size, and more risk factors for dissection have emerged, necessitating a multifactorial, individual approach. These data including z scores may add further information. However, the generalizability of these results requires further data.

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Bicuspid aortic valve (BAV) disease is frequent, occurring in 1% to 2% of the general population,¹ and is associated in roughly 50% of patients with dilatation of the ascending aorta (AA), the so-called “BAV aortopathy,” bearing an

increased risk for aortic dissection and rupture compared with the normal population.² Prophylactic surgery of the dilated AA potentially prevents these catastrophic events, but decision making is still of considerable debate and uncertainty for the patient and the surgeon, especially in patients with the primary indication for valve surgery.

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Abbreviations and Acronyms

AA	= ascending aorta
AAI	= ascending aorta intervention (AAR or AOP)
AAR	= ascending aorta replacement
AOP	= aortoplasty
BAV	= bicuspid aortic valve
BSA	= body surface area
HR	= hazard ratio
NOAI	= no aortic intervention
SE	= standard error

Guidelines for ascending aorta intervention (AAI) rely mainly on an absolute diameter of 45 mm for the AA³; they are certainly of great help for decision making but have specific shortcomings, eg, age as the most significant determinant for AA growth⁴ is not included. In addition, newer information suggests that the postdissection AA diameter, which was the basis for decision making, is significantly larger than the pre-dissection AA diameter⁵—the real diameter at risk. Furthermore, the diameter is only one of multiple factors causing rupture or dissection. These catastrophic events are the result of a complex interplay between aggravating or protective genes encoding the structural quality of the AA and environmental impacts, which are different in every patient.⁶

The use of more than simple aortic size criteria for an intervention decision on the AA toward an individualized approach seems theoretically advantageous and may be helpful to improve the results via fine-tuning the decision-making process. For 17 years, we have followed multifactorial decision making for the treatment of AA in patients with indication for BAV surgery, where age and body surface area (BSA) of the patients—determinants of the z score—and the diameter of the AA played major roles. Here, we present the results in 1693 patients with the primary indication of valve surgery and concretize our decision-making criteria with special reference to z scores of the AA diameter.

METHODS

Patients

Between February 1999 and December 2016, 1822 patients with BAV disease were operated on at our institution without an associated genetic syndrome (eg, Marfan syndrome, Ehlers–Danlos syndrome). In this study, we excluded 19 patients with type A dissection, 32 patients with endocarditis, 10 patients without valve surgery, and 68 patients with previous cardiac surgery. In all patients, the BAV type was classified according to a previous publication.⁷ Finally, the study group consisted of 1693 patients with BAV surgery and classified phenotypes of the BAV. Patient demographics, valve procedures, pre- and intraoperative data, and BAV phenotypes are presented in Tables 1 and 2. Follow-up was 99.5% complete and finalized in January 2017. The follow-up period ranged from 0 to 17.7 years (mean 7.0 ± 4.4 years) comprising 11,895 patient-years. There were 2 different groups of AA management: no aortic intervention (NOAI;

n = 1116) and AAI (n = 577) including aortoplasty (AOP; n = 173) and ascending aorta replacement (AAR; n = 404).

A reoperation on the AA was considered a reoperation when there was a primary indication for re-AAI like type A dissection or aneurysm or when the primary indication for reoperation was related to aortic valve dysfunction and the AA showed signs of increasing dimensions potentially leading to complications. There was one reoperation on an AA prosthesis in the AAR group with a primary valve indication and a kinking of the AA graft which was treated during valve reoperation. This kinking was not considered a potential complication and therefore was not included in reoperation group.

Data were collected via outpatient visits and questionnaires to the patient or family doctors. The study was approved by local ethics committee of University of Lübeck.

Surgery

The indication for valve surgery was based on the American College of Cardiology/American Heart Association Guidelines.⁸ The maximal diameter of the AA was measured preoperatively on computed tomography scan, angiogram, or echocardiogram and intraoperatively by direct measurement. The decision for AAR concomitant to the valve surgery was based on a multifactorial policy presented in detail elsewhere.⁹ In brief, the following factors were included: diameter of the AA around 45 mm, BSA, sex, age—more progressive decision in young age—fragility of the wall of the AA, progressive increase of AA diameter (0.5 cm per year), family history of aortic disease, BAV type 1 with insufficiency and BAV type 2/unicuspid, phenotype III and IV of AA according to Fazel and colleagues.¹⁶ Age, especially young age, was of special concern for decision making, because age is the most powerful determinant of growth and young age shows faster growth of AA diameters.⁴ AOP was performed in borderline dilatation of the lateral AA (Fazel type II), older age, no positive family history, no progressive growth of AA, normal-appearing quality of wall-tissue. The fragility of the wall tissue was assumed when (1) placement of the cannulation sutures and snaring tourniquets for cannula fixation caused bleeding and/or hematoma around the cannulation site; (2) stay sutures above the commissures showed unusual tearing through the wall; (3) aortotomy revealed thinning of the wall; and/or (4) a pale vasa vasorum-free area was present in the AA wall.⁹

The surgical technique consisted of standard cardiopulmonary bypass at 28°C perfusion hypothermia. A Dacron tube graft (DuPont, Wilmington, Del) was used for replacement of the AA in relation to the size of the patient, usually 28 to 32 mm in diameter. It was up to the discretion of the surgeon to use a preformed curved AA prosthesis (B. Braun Melsungen AG, Melsungen, Germany). In case of supracommissural AAR, the distal and proximal suture lines were reinforced with a strip of Teflon felt. In 65 cases, hemiarch replacement was necessary and performed during 18°C hypothermia for 20 minutes followed by antegrade cerebral perfusion if necessary. AOP consisted of plicating the AA at the eccentric dilatation between 2 Teflon felts.⁹

Statistical Analysis

Data are presented as absolute numbers, relative frequencies, and as mean and standard deviation respectively. Comparisons between the groups were performed with the χ^2 test, the Mann-Whitney *U* test, and the Student *t* test, where appropriate. For all analyses, $P < .05$ was considered to be statistically significant. The calculations were performed with IBM SPSS Statistics Version 22.0.0.2 (IBM Corp., Armonk, NY).

Both in-hospital deaths and late deaths were included into survival analyses. The Kaplan-Meier method and the log-rank test were used to provide a basic comparison of survival and reoperation for the different procedures. The Cox proportional hazards model, fitted with SAS 9.4 (SAS Institute, Cary, NC), was used to compare survival for the 3 procedures (NOAI, AAR, AOP) while also allowing for other variables, such as age at operation. The survival of patients in the study was compared with the predicted survival experience for equivalent members of the general population with respect to age and sex. The latter was determined using the German life-table, 2010/2012 (www.destatis.de). The subject-years

TABLE 1. Patient demographics (n = 1693)

	NOAI (n = 1116)	AAI (AAR + AOP) (n = 577)	AAR (n = 404)	AOP (n = 173)	P value NOAI vs AAI
Age, y					<.001
Mean ± SD	59.0 ± 15.0	54.3 ± 13.8	53.0 ± 13.4	57.2 ± 14.2	
Min-max	16.2-87.2	15.2-85.3	15.4-81.6	15.2-85.3	
BSA, m ²					.007
Mean ± SD	1.96 ± 0.2	1.99 ± 0.22	2.00 ± 0.21	1.98 ± 0.22	
Min-max	1.36-2.74	1.35-2.80	1.48-2.80	1.35-2.42	
Male sex	847 (75.9)	434 (75.2)	307 (76.0)	127 (73.4)	.765
BAV type					<.001
0	104 (9.3)	57 (9.9)	45 (11.1)	12 (6.9)	
1	896 (80.3)	407 (70.5)	266 (65.8)	141 (81.5)	
2	116 (10.4)	113 (19.6)	93 (23)	20 (11.6)	
Hypertension	789 (70.7)	359 (62.2)	247 (61.1)	112 (64.7)	<.001
LVEF					.230
<30%	36 (3.2)	14 (2.4)	9 (2.2)	5 (2.9)	
30%-50%	192 (17.2)	87 (15.1)	60 (14.9)	27 (15.6)	
>50%	855 (76.6)	465 (80.6)	327 (80.9)	138 (79.8)	
Unknown	33 (3)	11 (1.9)	8 (2)	3 (1.7)	
NYHA class					.001
I	218 (19.5)	142 (24.6)	106 (26.2)	36 (20.8)	
II	378 (33.9)	224 (38.8)	162 (40.1)	62 (35.8)	
III	420 (37.6)	178 (30.8)	115 (28.5)	63 (36.4)	
IV	45 (4)	16 (2.8)	8 (2)	8 (4.6)	
Unknown	55 (4.9)	17 (2.9)	13 (3.2)	4 (2.3)	
Diabetes	168 (15.1)	41 (7.1)	23 (5.7)	18 (10.4)	<.001
COPD	86 (7.7)	32 (5.5)	17 (4.2)	15 (8.7)	.107

Values in bold indicate statistical significance. *NOAI*, No aortic intervention; *AAI*, ascending aorta intervention; *AAR*, ascending aorta replacement; *AOP*, aortoplasty; *SD*, standard deviation; *BSA*, body surface area; *BAV*, bicuspid aortic valve; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease.

method was used to compare the numbers of deaths for the procedures with the expected (ie, average) numbers of deaths in the general population with the same age and sex profile. Univariate variables with a $P < .1$ were considered in the multivariable analysis followed by a backward elimination procedure. Several parameters were used for decision making on AA treatment (see the preceding section, "Surgery") including quantitative factors and also qualitative ones. All parameters are indicating some kind of pathology of the AA. The question was: Which parameter is present and most relevant in every patient? That was the z score of the AA diameter¹⁰ at the time of decision making for the operation. This decision diameter also was influenced by the presence of the aforementioned parameters, eg, a patient with aortic insufficiency and BAV type 1 got an AAI at lower AA diameter resulting in a lower decision z score; the same holds true for patients with family history or tissue frailty. Therefore, the retrospectively determined decision z score is the essence of all parameters used for decision making in a single patient.

The z scores of the AA diameter were calculated, taking into consideration the absolute AA diameter as well as age, BSA, and sex. The z score for each patient was calculated by determining the difference between patient's AA diameter and the age-, BSA-, and sex-matched mean normal AA diameter, divided by the standard deviation. Normal mean diameters and standard deviations were deduced from Biaggi and colleagues.⁴ To investigate the z score decision boundary for AAI nonparametric machine learning methods (support vector machines) were used.¹¹ For this analysis, we chose a probability of 0.6 for performing an AAI so that the decision boundary corresponds to a slightly greater probability for intervention than in the case of equiprobable classes.

These calculations were performed with R version 3.3.3 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org/>). Receiver operating characteristic curve analysis was performed to validate the z score decision model.¹²

To provide a nomogram based on diameter and age for different BSAs (Figure 4), we generated the threshold for intervention on the AA (blue lines) from the z score thresholds in Figure 3 as follows:

$$\frac{(p-m)z}{1.645} + m$$

Where P = 95th percentile of the mean normal diameter⁴; m = mean normal diameter; z = age dependent z-score threshold value from Figure 3; the divisor of 1.645 is the corresponding z-score of the 95th percentile.

RESULTS

Hospital Mortality and Morbidity

The hospital mortality and morbidity are presented in Table 3 and did not differ significantly between the 3 AA treatment groups and between NOAI and AAI. In-hospital death was 1.2% ($n = 13$) in the NOAI group and 0.9% ($n = 5$) in the AAI group. Causes of in-hospital death were cardiac in 11 (61.1%) and noncardiac in 7 (38.9%) patients and did not differ between the groups ($P = .203$). In both groups, one patient was operated on an emergency basis.

TABLE 2. Operative data (n = 1693)

	NOAI (n = 1116)	AAI (AAR + AOP) (n = 577)	AAR (n = 404)	AOP (n = 173)	P value NOAI vs AAI
AA diameter, mm					<.001
Mean ± SD	36.6 ± 5.1	49.9 ± 7.1	51.3 ± 7.3	46.5 ± 4.9	
Median	37	50	51	46	
Min-max	20-51	29-84	29-84	35-65	
Z score	0.9 ± 1.7	5.3 ± 2.5	5.9 ± 2.6	4.0 ± 1.8	<.001
Aortic valve lesion					<.001
Stenosis	516 (46.2)	181 (31.4)	111 (27.5)	70 (40.5)	
Insufficiency	186 (16.7)	146 (25.3)	115 (28.5)	31 (17.9)	
Combined	414 (37.1)	250 (43.3)	178 (44.1)	72 (41.6)	
Aortic valve procedure					<.001
Repair	97 (8.7)	77 (13.3)	68 (16.8)	9 (5.2)	
Ross	211 (18.9)	151 (26.2)	94 (23.3)	57 (32.9)	
Biological valve	611 (54.7)	209 (36.2)	137 (33.9)	72 (41.6)	
Mechanical valve	197 (17.7)	140 (24.3)	105 (26)	35 (20.2)	
Bypass time, min					<.001
Mean ± SD	139.2 ± 56.8	181.0 ± 62.8	191.2 ± 59.5	157.0 ± 64.2	
Min-max	45-417	39-493	85-493	39-299	
Crossclamp time, min					<.001
Mean ± SD	113.4 ± 50.0	147.9 ± 55.5	155.8 ± 52.4	129.2 ± 58.4	
Min-max	29-297	29-357	59-357	29-264	
Mitral valve surgery	50 (4.5)	20 (3.5)	12 (3.0)	8 (4.6)	.368
Tricuspid valve surgery	10 (0.9)	8 (1.4)	6 (1.5)	2 (1.2)	.453
CABG	218 (19.5)	56 (9.7)	34 (8.4)	22 (12.7)	<.001
Hemiarch replacement	0	65 (11.3)	65 (16.1)	0	<.001
Aortic root intervention					<.001
Root repair	33 (3)	70 (12.1)	50 (12.4)	20 (11.6)	
Bentall	4 (0.4)	82 (14.2)	82 (20.3)	0	
David	18 (1.6)	40 (6.9)	39 (9.7)	1 (0.6)	
Yacoub	2 (0.2)	22 (3.8)	21 (5.2)	1 (0.6)	

Values in bold indicate statistical significance. NOAI, No aortic intervention; AAI, ascending aorta intervention; AAR, ascending aorta replacement; AOP, aortoplasty; AA, ascending aorta; SD, standard deviation; CABG, coronary artery bypass graft.

Overall Mortality

Cox proportional hazards model revealed age ($P < .001$, hazard ratio [HR] 1.093, standard error [SE] 0.00845) but not female sex ($P = .241$, HR 0.784, SE 0.20711), AAI ($P = .199$, HR 0.716, SE 0.26025), and AA diameter ($P = .255$, HR 1.015, SE 0.01323) as a significant risk factor for survival time. Once age was included in the model, there

was no difference among the 3 treatment groups in survival. When matched for age and sex follow-up profile in the general population, the survival in the whole study group was reduced significantly ($P < .001$). When differentiating between AA treatment groups, the NOAI group showed a somewhat more reduced survival compared with the general population ($P < .001$), whereas in the AAI group the

TABLE 3. Postoperative outcome (≤30 days)

	NOAI (n = 1116)	AAI (AAR + AOP) (n = 577)	AAR (n = 404)	AOP (n = 173)	P value NOAI vs AAI
Death	13 (1.2)	5 (0.9)	4 (1.0)	1 (0.6)	.629
IABP	24 (2.2)	9 (1.6)	8 (2.0)	1 (0.6)	.463
Dialysis	38 (3.4)	11 (1.9)	6 (1.5)	5 (2.9)	.093
ICU stay >72 h	106 (9.5)	59 (10.2)	43 (10.6)	16 (9.2)	.666
Permanent stroke 72 h	7 (0.6)	3 (0.5)	2 (0.5)	1 (0.6)	1.000

NOAI, No aortic intervention; AAI, ascending aorta intervention; AAR, ascending aorta replacement; AOP, aortoplasty; IABP, intra-aortic balloon pump; ICU, intensive care unit.

survival was reduced but not by such a great margin and the evidence of a difference from the general population was not significant ($P = .27$) (Figure 1). The standardized mortality ratios calculated by the subject years-method were 1.27 (95% confidence interval, 1.10-1.45, $P < .001$) for NOAI and 1.16 (95% confidence interval, 0.88-1.44, $P = .27$) for AAI.

Univariate risk factors of shorter survival are shown in Table E1. Multivariable analysis revealed age, lower ejection fraction, chronic obstructive pulmonary disease, and dialysis as risk factors for death and the Ross operation for better survival. The causes of death were cardiac in 81 (30.7%) patients (NOAI, $n = 62$ [31.2%]; AAI, $n = 19$ [29.2%]), noncardiac in 155 (58.7%) patients (NOAI, $n = 115$ [57.8%]; AAI, $n = 40$ [61.5%]), and unknown in 28 (10.6%) patients (NOAI, $n = 22$ [11.1%]; AAI, $n = 6$ [9.2%]). The difference between the three groups regarding the cause of death was not significant ($P = .978$).

Reoperation

Reoperations are depicted in Table E2. In the AAR group, there was no reoperation but six reoperations in the AOP and NOAI group either. Freedom from

reoperation was significantly lower ($P = .002$) in AOP compared with NOAI (Figure 2). Two acute type A dissections occurred on patients with BAV type 1 LR and aortic valve insufficiency. Reoperations on the aortic valve were necessary in 47 (4.2%), 11 (2.7%), and 10 (5.8%) patients in the NOAI, AAR, and AOP group, respectively ($P = .196$).

Z-Score Analysis

There was significant evidence that the decision to perform an AAI was dependent on the age and the z score of the patient. The age-related z score thresholds for the aortic interventions are displayed in Figure 3, with greater z thresholds in younger patients. Figure 4 gives decision thresholds for AA treatment based on the z-score threshold of Figure 3. The area under the receiver operating characteristic curve was 0.945.

A total of 44% of patients presenting with pure aortic valve insufficiency received an AAI compared with 26% in patients with aortic valve stenosis. When compared with the guideline of 45 mm, 97 patients (8% of 1213 patients with an AA diameter <45 mm, representing 16.8% of the AAI group) received a more prophylactic AAI.

FIGURE 1. Survival curves for the NOAI and AAI groups (solid lines) and their age and gender matched general population (dashed lines) (NOAI, $P < .001$; AAI, $P = .27$). The shaded areas represent the 95% confidence intervals. NOAI, No aortic intervention; AAI, ascending aorta intervention.

FIGURE 2. Freedom from reoperation curves for NOAI and AOP. There was no reoperation in the AAR group. The shaded areas represent the 95% confidence intervals. Data beyond the dashed line were statistically not relevant because the numbers at risk were lower than 10% of the initial sample size. NOAI, No aortic intervention; AAI, ascending aorta intervention.

DISCUSSION

Decision making for AA treatment when the thorax will be opened for BAV surgery is controversial. The surgical aim is to prevent catastrophic rupture or dissection by prophylactic surgery without increasing the procedural risk.

Rupture or dissection occurs when the wall stress exceeds tensile strength. Wall stress can be approximated by the Law of Laplace: $(\text{pressure} \times \text{diameter}) \div \text{wall thickness}$, reflecting the basic principle of nature: The interplay between genetic predisposition and external impact.⁶ Out of these parameters, the AA diameter is the most practical to measure and does not change immediately serving as the definite parameter for decision making in the real world. Guidelines recommend a diameter of 45 mm for aortic repair in BAV surgery.³ These guidelines are helpful but carry different shortcomings and uncertainties. The AA diameter normally increases with growth and age¹³ more than to BSA, and the diameter grows faster in early adulthood compared with older age.^{4,14} These facts lead to concerning issues: a diameter of 40 mm at the age of 25 years is more pathologic than the same diameter at age

75 years,¹⁰ or in a 25-year-old woman with a BSA of 1.6 m², the expected mean normal AA diameter is 26.9 mm,⁴ a 50% increase of this diameter, which is the definition of an aneurysm,¹⁵ results in a diameter of 40.4 mm. Following the guidelines, this AA would be left in place during BAV surgery, demonstrating that a fixed aortic size criterion may deserve special consideration. The question is: Can we adapt this diameter to the heterogeneity of patients' conditions for a more individualized treatment strategy? At the moment, there are no individual risk factors that would allow for a strict personalized treatment policy, but there are proliferating data focusing on risk clusters that may initiate this way for a more tailored decision process than a simple absolute diameter.

If we agree that the "normal" diameter is the optimal diameter warranting the lowest risk of rupture and dissection, then we should relate the individual AA diameter of a patient to the "normal" diameter that can be done by the z score. We concretized our 17 years' experience of decision making with respect to the z score threshold of AA intervention and found that it varies during age (Figure 3),

FIGURE 3. Plot of z-score thresholds (for NOAI and AAI) with respect to patients' age (for details see section "Statistical Analysis"). White points represent patients who received an AAI; black points patients with NOAI. AA, Ascending aorta.

with a greater z score at younger age. These AA z score-derived threshold diameters were lower than the 45-mm threshold of the guidelines in younger patients (Figure 4). Thus, 97 patients (8% of 1213) had more prophylactic AAI.

There is increasing evidence supporting this strategy. Aortic insufficiency has a 10-fold risk of dissection,¹⁶ probably related to the more pathologic wall histology of the AA in these patients.¹⁷ Whether this is related to a maturation defect of the AA wall tissue in these young patients remains speculative.¹⁸ The relevance of aortic valve insufficiency in our decision-making process is indicated by the fact that 44% of patients presenting with pure aortic valve insufficiency received an AAI compared with 26% in the aortic valve stenosis group. Two patients of this series experienced later acute type A dissection who had initially aortic insufficiency (Table E2). Probably a more aggressive approach using AAR could have had prevented these dramatic events.

That aortic insufficiency indicates some kind of connective tissue weakness is further supported by the fact that aortic insufficiency in BAV results from prolapsing leaflet tissue of the cusps is related to an elongated anterior mitral leaflet, is a predictor of faster AA growth, and is often related to Fazel type IV AA dilatation with a lack of the sinutubular junction.¹⁹⁻²¹ Probably progressive growth, family history, aortic insufficiency, fragile tissue, complex AA dilatation including root, and AA indicate different but coherent items of a genetically determined connective tissue weakness, which are less resilient to external impact like pressure. This is in contrast to AA wall tissue

in BAV with calcified valve stenosis mostly presenting with local dilatation at the convexity which is probably related to BAV intrinsic flow phenomena.²² In many patients, the AA remains normal in diameter despite abnormal BAV-related shear stress impact on the wall, indicating the heterogeneity in genetic development.

Also, newer information on the real diameter at risk for rupture or dissection supports the more liberal concept in selected patients: The International Registry of Acute Aortic Dissection (IRAD) study showed that 40% of patients with dissection had diameters less than 50 mm,²³ and recently Rylski and colleagues⁵ reported that the pre-dissection diameter—which should be the real diameter for risk estimation—was only 40.1 mm (36.6-45.3) compared with the postdissection diameter of 52.9 mm (46.1-58.6), demonstrating that the diameter at risk is approximately 40 mm and significantly lower than usually thought. This is of particular interest in younger patients because of their long life expectancy. In these young patients, the AA after valve intervention will grow with patient- and hemodynamic-specific variable progression over a long life span and potentially and unpredictably reaching sooner or later a more "risky" area necessitating continuous surveillance and new decision making on AA treatment as a redo. In this respect, the report of Kinoshita and colleagues²⁴ is of interest, showing that an AA diameter greater than 40 mm at aortic valve replacement emerged as a significant predictor for dilatation later on. This supports earlier experience showing that 25% of patients with AA diameter greater than 40 mm and aortic valve surgery for aortic insufficiency required a subsequent AA surgery.²⁵ In contrast, Kim and colleagues²⁶ showed in a large database that the risk for dissection was low for diameters less than 5.5 cm when elective surgery was performed in time. However, follow-up was short, with a median time of 40 months. Thus, the risk estimates are relatively conservative because with longer follow-up the diameter is increasing and the risk also. Nevertheless, female sex and BAV turned out to be significant risk factors for aortic expansion.

Beside potential benefits of a more liberal approach, especially in the younger age group, the crucial issue is its risk. The hospital mortality and morbidity were low in the AAI group as also shown by Lima and colleagues²⁷ and Svensson and colleagues.²⁸ It must be considered that the patients' characteristics showed less baseline risk for patients undergoing AAI, which could have introduced some bias regarding mortality and needs further evaluation in a larger group of patients. There was no death in the 55 patients 35 years of age or younger in the AAI group. Furthermore, early mortality and morbidity were not increased compared with the NOAI group, supporting the results published by Svensson and colleagues.²⁸ All 5 patients who died in the AAI group had an AA diameter of 45 mm or larger and thus did not originate from the more

FIGURE 4. Our institutional guidelines for decision making on ascending aorta intervention in BAV surgery. The blue lines represent the decision thresholds for different BSAs in relation to age and ascending aorta diameter, which was more liberal if patients had aortic insufficiency with BAV type 1, BAV type 2/unicuspid, phenotype III or IV according to Fazel, family history of aortic complications, progressive growth of AA (0.5 cm/y), and fragility of the wall. Red area: More liberal approach compared to guidelines of 45 mm. Red lines: guidelines threshold diameter of 45 mm; blue lines: z score–based threshold diameter; green lines: mean normal diameter. BSA, Body surface area.

liberal approach group. Also, longer-term survival was not influenced negatively by AAI versus NOAI ($P = .199$). Compared with the adjusted general population, survival was lower for the NOAI group ($P < .001$) and also for AAI ($P = .27$), but not by such a large margin and not significantly for the AAI group. However, the number of events and patients is relatively small, and the risk factors for death were not so pronounced in the AAI group compared with the NOAI group. Thus, these promising

survival data have to be considered with caution and need further evaluation. This issue includes another uncertainty that is the lack of knowing how many deaths were related to rupture or dissection. There was no autopsy, so it cannot be excluded that especially in the NOAI and AOP groups dissections and fatal rupture occurred albeit undetected which was less likely in the AAR group, although there was no difference in the causes of death (cardiac vs noncardiac) between groups ($P = .978$). Nevertheless, if late death

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Longer-term results, z-scores and a decision nomogram after treatment of the ascending aorta in 1693 bicuspid aortic valve operations

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VIDEO 1. Longer-term results, z scores, and decision nomograms for treatment of the ascending aorta in 1693 bicuspid aortic valve operations. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)31907-4/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)31907-4/fulltext).

in the NOAI group was related to AA problems, survival in this patient group may be improved by adjusted cutoffs for intervention. Furthermore, risk factors for mortality were related exclusively to other parameters than AAI, such as preoperative ejection fraction, high New York Heart Association class, chronic obstructive pulmonary disease, intra-aortic balloon pump (only in univariate analysis), and diabetes (Table E1).

Interestingly, if we calculate the cross-sectional area/height ratio in our patients, the threshold (mean ratio minus standard deviation) for AAI was $8 \text{ cm}^2/\text{m}$, which is in agreement with the report of Svensson and colleagues,²⁸ who recommended an indication for AAR between a ratio greater than 8 to $10 \text{ cm}^2/\text{m}$.^{28,29} However, this ratio does not consider younger age of the patients, which is of special concern in the decision-making process.

There were 6 reoperations in the NOAI group, including 1 acute type A dissection. According to the nomogram this patient (male, age 42 years, AA diameter 43 mm, BSA 2.1 m^2 , and aortic insufficiency with BAV type 1) should have had AAI. With longer follow-up duration, probably more events will occur so that the validity of the z-score analysis may become more precise. There was no reoperation in the AAR group, as a sign for a more definite approach. Thus, AAR provides the greatest protection against AA complications in the future, which is of particular interest in young patients with a long life expectancy and active (blood pressure increase) lifestyle. The reoperation rate was greatest in the AOP group, indicating that our technique of AOP does not prevent future dilatation and complications in all patients. All patients who were reoperated on the AA as the primary indication for reoperation had a diameter of 45 mm or more at the first operation (Table E2). Probably in these patients, an AAR would have been

the better solution than the AOP, especially if aortic insufficiency was the primary valve lesion.

Nevertheless, the average increase in diameter after AOP did not show to be more progressive than the AA diameter increase in patients without AOP.³⁰ Maybe our technique of AOP was not perfect or the remaining wall tissue is less resilient in certain patients, especially in those with aortic insufficiency.³¹ Because of the reoperations performed and those probably to come in the follow-up time, careful surveillance of patients undergoing AOP is necessary and the indication for AOP needs more restriction or should be abandoned at all because AAR showed best results and carried minimal increased surgical risk. Nevertheless, the argument of preserving the Windkessel function with AOP may turn out later in life to be beneficial for left ventricular function.

This report includes the results of our 17 years of institutional experience only; the results are not generalizable. We advocate the use of these novel guidelines only if a low hospital mortality of less than 1% for AAI is warranted. As shown in Figure 4, these guidelines are predominantly more liberal in younger and female patients. Interestingly this policy finds some support in the article published by Kim and colleagues,²⁶ who showed that female sex and BAV were independent risk factors of aortic expansion.

As a perspective analysis, it is of great importance to routinely follow the AA diameter in the patients with NOAI, especially with respect to valve phenotype and hemodynamics, which could be used to further refine the decision-making process.

Limitations

This study is retrospective and not randomized, but randomization is difficult because there is most likely no increase of early or late mortality and morbidity related to AAI versus NOAI and the primary endpoint of a study would be dissection or rupture. Furthermore, the causes of death are not known in a lot of patients because of a lack of autopsy; thus, there may be several fatal dissections and ruptures left undetected. In the NOAI cardiac death group ($n = 62$) there were 11 (18%) sudden deaths. Whether these were related to AA problems remains speculative. In the AAI group, there was 1 sudden death out of 19 cardiac deaths (5%). However, because we have no autopsies, this item of sudden death as a surrogate for dissection seems too vague for further analysis of the “risk versus benefit” item. An important issue is the fact that the criteria for decision making for AAR other than the 45-mm guidelines threshold were somewhat subjective and extracted more or less from existing knowledge like exponential diameter growth, especially in young subjects and experience like frail tissue and more general enlargement of the root and AA in patients with aortic valve insufficiency. Not only the different parameters for decision making could

have introduced certain bias but also the fact that 12 surgeons performed 95% of the procedures. However, all these surgeons were trained to do the operation in the same fashion.

Furthermore, it is not known whether the age-related dilatation of the AA is a normal or a degenerative process. However, from an epidemiologic standpoint, because this change takes place in all patients and because aortic events are extremely rare in the general population, this increase of AA diameters with age should be taken into consideration in defining “normal.” Because the decision z score was analyzed retrospectively, all decision parameters besides the AA diameter had an influence on this z score, making it difficult to figure out the quantitative relevance of one of these parameters on decision making.

CONCLUSIONS

In our study, AAI could be performed with low hospital mortality and obviously did not add to the overall mortality compared with NOAI. AAR was the most definite intervention. The multifactorial decision for AAI including the z score of the AA was more liberal in younger patients compared with the simple aortic size guidelines and provided excellent results (Video 1). However, generalizability necessitates further data.

Conflicts of Interest Statement

Hans-H. Sievers, MD, received royalties from B. Braun Melsungen (Melsungen, Germany) for curved aortic prostheses and sinus prostheses. All other authors have nothing to disclose with regard to commercial support.

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Key Words: bicuspid aortic valve, aortopathy, nomogram, z-score, long-term results, ascending aorta

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TABLE E1. Univariate risk factors for survival time using the Cox proportional hazards model matched for age, sex, and AAI

Variable	P value	Hazard ratio	95% Confidence interval
BAV			
Type 1		Reference	
Type 0	.714	1.088	0.637-1.539
Type 2/unicuspid	.403	0.750	0.078-1.422
Height	.993	1.000	0.98-1.02
Weight	.508	0.997	0.987-1.007
LVEF			
>50%		Reference	
30%-50%	.004	1.538	1.246-1.83
<30%	<.0001	2.873	2.397-3.349
Hypertension	.141	1.251	0.953-1.549
NYHA class			
III or IV		Reference	
II	.007	0.664	0.364-0.964
I	.003	0.534	0.12-0.948
Diabetes	.028	1.401	1.099-1.703
COPD	.0001	1.887	1.56-2.214
Aortic valve lesion			
Stenosis		Reference	
Insufficiency	.409	0.824	0.365-1.283
Combined lesion	.405	0.893	0.628-1.158
Aortic valve procedure			
Biological valve		Reference	
Repair	.100	0.502	−0.319 to 1.323
Ross	.001	0.352	−0.277 to 0.981
Mechanical	.252	0.792	0.392-1.192
Bypass time*	.700	0.925	0.531-1.319
Crossclamp time*	.440	0.869	0.512-1.226
Mitral valve surgery	.121	1.557	0.996-2.118
Tricuspid valve surgery	.090	2.358	1.364-3.352
CABG	.836	1.032	0.736-1.328
Aortic root intervention	.458	1.182	0.741-1.623
Body surface area	.457	0.734	−0.081 to 1.549
IABP	.001	3.035	2.365-3.705
Dialysis	<.0001	4.774	4.37-5.178

Values in bold indicate statistical significance. BAV, Bicuspid aortic valve; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump. *Natural logarithms have been taken.

TABLE E2. Reoperation

Data of primary operation							Data of reoperation				
AA intervention	AV intervention	Concomitant procedure	Age, y	Sex	BAV type	AA diameter, mm	Z score	Time to reoperation, y	AA diameter	Indication for reoperation	Operation
AOP	AVR-M	None	62.1	Male	1 LR, I	49	3.93	7.1	61	Type A dissection	Bentall, AAR, hemiarch
AOP	AVR-B	MAZE	74.1	Male	1 NL, S	47	2.72	0.3	N/A	Infection of prosthetic material	AAR (homograft)
AOP	Ross	None	52.9	Male	1 LR, I	46	3.87	11.2	52	AA aneurysm	AAR, hemiarch
AOP	AVR-B	None	58.1	Female	1 LR, S	45	3.62	9.5	43	AV insufficiency, AA aneurysm	AAR, AVR-B
AOP	Repair	None	37.6	Male	1 RN, I	47	4.93	7.8	54	AA aneurysm, combined AV lesion	AAR, hemiarch, AVR-M
AOP	AVR-M	CABG	68.1	Male	1 LR, S	52	4.43	4.5	58	AA aneurysm	AAR
NOAI	AVR-B	CABG	69.5	Male	1 LR, C	35	−0.41	1 d	N/A	Perforation of the AA 1 cm above bypass anastomosis	Perforation closure
NOAI	AVR-B	None	52.0	Male	1 LR, S	43	3.16	2.8	45	AV endocarditis, AA enlargement	AVR-B, root replacement, AOP
NOAI*	AVR-B	None	56.9	Male	1 RN, S	43	2.22	1.9	50	AV insufficiency, suture line disruption, AA aneurysm	Bentall, AAR
NOAI	AVR-B	MVR, partial decalcification of AA and LA	69.9	Female	1 RN, S	N/A	N/A	0.8	120	False aneurysm at aortotomy	AAR
NOAI	Repair	None	29.8	Male	1 LR, I	40	3.59	8.3	43	Combined AV lesion, AA dilatation	Ross, AAR
NOAI	AVR-M	None	42.1	Male	1 LR, I	43	3.45	12.2	–	Type A dissection	Bentall, AAR

Bold text indicates primary indication for reoperation. AA, Ascending aorta; AV, aortic valve; BAV, bicuspid aortic valve; AOP, aortoplasty; AVR, aortic valve replacement; M, mechanical valve; LR, left coronary sinus/right coronary sinus; I, insufficiency; AAR, ascending aorta replacement; B, biological valve; S, stenosis; N/A, not available; CABG, coronary artery bypass surgery; C, combined lesion; RN, right coronary sinus/noncoronary sinus; MVR, mitral valve replacement; LA, left atrium; NOAI, no aortic intervention. *This patient had several AV reoperations before AA reoperation: the first reoperation occurred 70 days after primary operation because of AV endocarditis with AV replacement with biological valve and reconstruction of the annulus; the second reoperation occurred 346 days after primary reoperation because of AV endocarditis with AV replacement with biological valve; for the third reoperation, see table.